Empirical treatment of IFI in fever and neutropenia

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leukemia
acute
blood
medical
leukocyte
clinical
immune
lymphoblastic
macrocyte
membranes
medicine
therapy
antigen
health
lymphocyte
eosinophil
segmented
treatment
myeloblastic
diagnosis
myelogenous
leukemic
lab
myeloblast
neoplasm
monocyte
microscope
smear
decrease
infection
bactericidal
bone
myelocyte
lobed
hematology
system
examine
promyelocyte
abnormal
hospital
cytology
microcyte
microscopic
death
illness
human
chemotherapy
pathology
cancer
malignancy
cml
lymphoma
body
granulation
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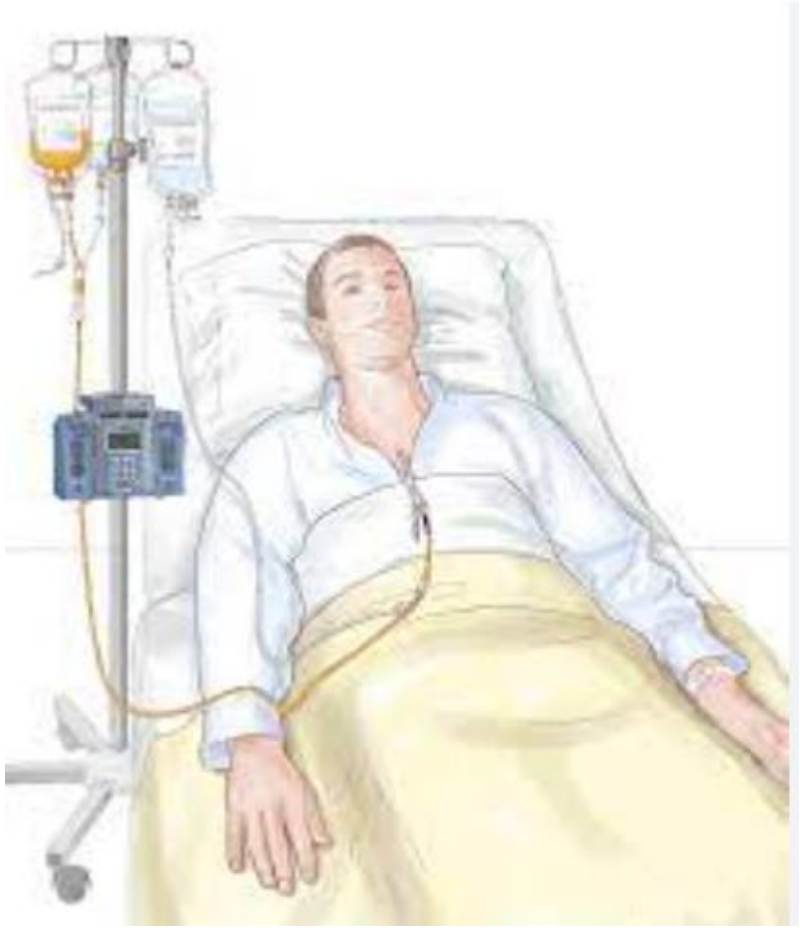
microbiology
chronic
marrow
care
nucleus
anemia
myeloid
laboratory
monocytic
examinations
metastases

Case Report



بیمار آقای ۳۸ ساله مبتلا به AML بدون بیماری زمینه ای در یکی از بیمارستان های دانشگاه علوم پزشکی شهید بهشتی بستری است.

- بیمار برای اولین بار تحت کموتراپی قرار گرفته است، برای بیمار درخواست مشاوره عفونی می شود در شرح حال بیمار سابقه مصرف فلوکونازول را می دهد.
- بیمار در بخش به طور ناگهانی دچار تب و لرز شده و در معاینه موکوزیت ندارد.
- تاکی پنه، تاکیکاردی و افت فشار خون دارد.
- در بررسی آزمایشگاهی ANC<200 دارد.

علاوه بر اقدامات اولیه تشخیصی:

۱- برای این بیمار **درمان آنتی بیوتیک امپریکال** مناسب کدام است؟

۲- جهت وی **درمان امپریکال ضد قارچ** مناسب کدام است؟

Inappropriate Empirical Antibiotic Treatment in Highrisk Neutropenic Patients With Bacteremia in the Era of Multidrug Resistance

Bloodstream infection epidemiology in patients with febrile neutropenia (FN) has been changing in the last few decades:

- Significant decrease in gram-positive cocci (GPC)
- Increase in gram-negative bacilli (GNB)
- A progressive rise in multidrug-resistant (MDR) strains

Inappropriate Empirical Antibiotic Treatment in Highrisk Neutropenic Patients With Bacteremia in the Era of Multidrug Resistance

During the study period, 1615 episodes of BSI in 1309 oncohematological patients with high-risk FN were documented:

- Gram-negative microorganisms accounted for **56%** of cases.
- Gram-positive microorganisms for **43%**.
- Candidemia was found in **3%** of episodes
- Polymicrobial bacteremia represented **11%** of all cases.
- The most frequently isolated microorganism was Escherichia coli (**24%**), followed by coagulase-negative staphylococci (CoNS) (**21%**) and P. aeruginosa (**16%**).

Inappropriate Empirical Antibiotic Treatment in Highrisk Neutropenic Patients With Bacteremia in the Era of Multidrug Resistance

- Overall, 221 (**14%**) MDR GNB were isolated, accounting for **24%** of all GNB episodes. Likewise, **28%** of P. aeruginosa isolates were MDR.
- Among E. coli and Klebsiella species isolates, **20%** and **22%** were extended-spectrum β-lactamase (ESBL) producers, respectively.
- Only 2 (**0.2%**) carbapenemase-producing Enterobacteriaceae were found over the whole study period.
- Among the 71 MDR P. aeruginosa isolates, all were resistant to fluoroquinolones, **96%** were resistant to piperacillin-tazobactam, **90%** to carbapenems, and **90%** were resistant to antipseudomonal cephalosporins.
- Only **11%** were resistant to amikacin.

Current spectrum of bacterial infections in patients with nosocomial fever and neutropenia

67% of the organisms were gram negative, 29.8% gram positive, and 3.2% polymicrobial:

- Pseudomonas aeruginosa
- Acinetobacter baumannii
- Klebsiella pneumonia

29.8% of the organisms were gram positive:

- Coagulase positive staphylococci
- Coagulase negative staphylococci

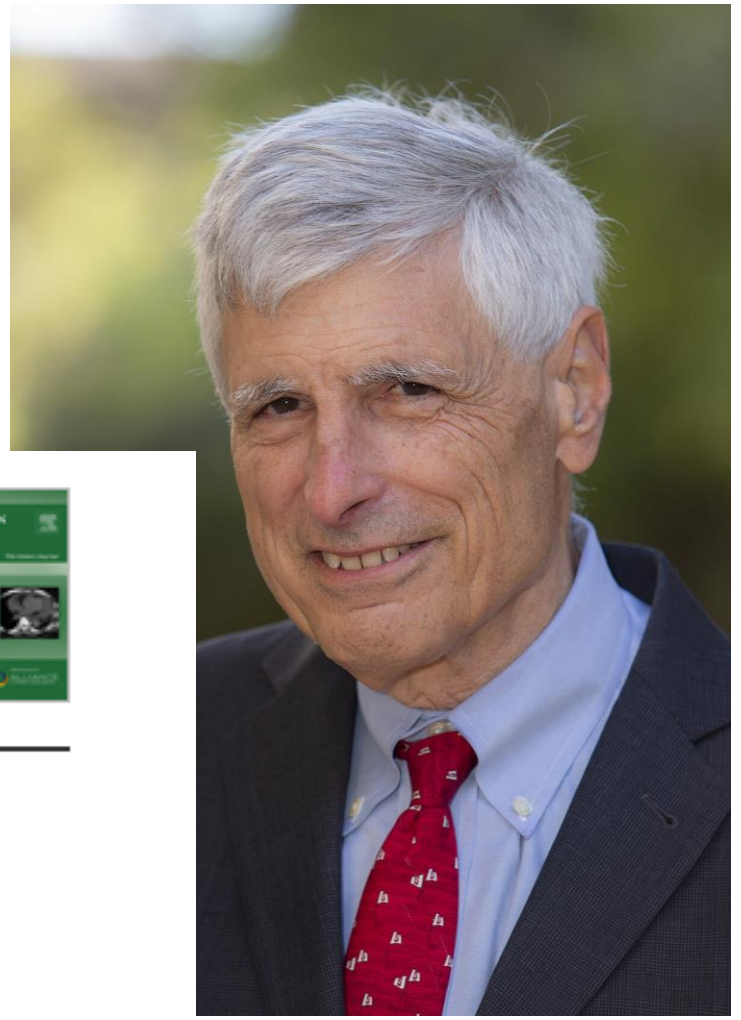
3.2% of the organisms were polymicrobial

Current spectrum of bacterial infections in patients with nosocomial fever and neutropenia

The Frequency (Percentage) of Pathogens in Nosocomial Fever and Neutropenia

	N	Percentage
Escherichia coli	27	27.6 %
Pseudomonas aeruginosa	16	16.3 %
Acinetobacter baumanii	12	12.2 %
Klebsiella pneumoniae	8	8.2 %
Coagulase positive staphylococci	8	8.2 %
Coagulase negative staphylococci	8	8.2 %
Enterococcus faecalis	6	6.1 %
Staphylococcus aureus	5	5.1 %
Enterobacter aerogenes	4	4.1 %
Streptococcus pneumoniae	2	2 %
Salmonella typhimurium	1	1 %
Yeast	1	1 %
Total	98*	100 %

* Total number of organisms is assumed after considering polymicrobial infections



ELSEVIER

The American Journal of Medicine

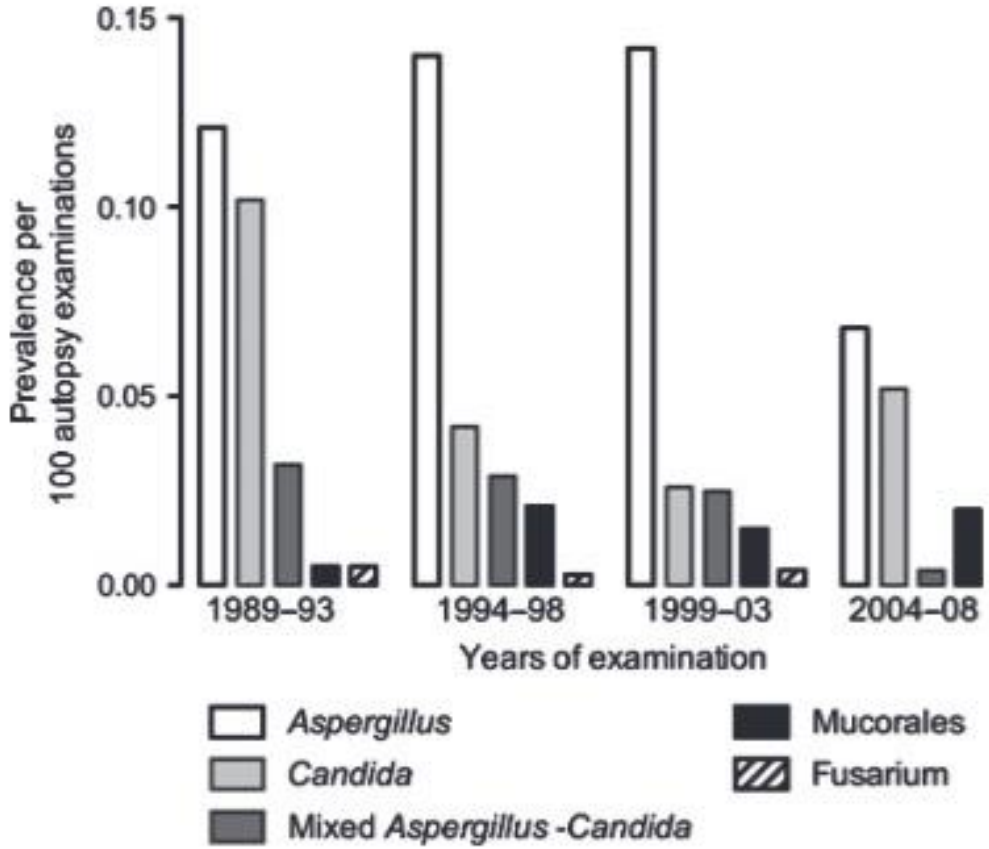
Volume 72, Issue 1, January 1982, Pages 101-111

Clinical study

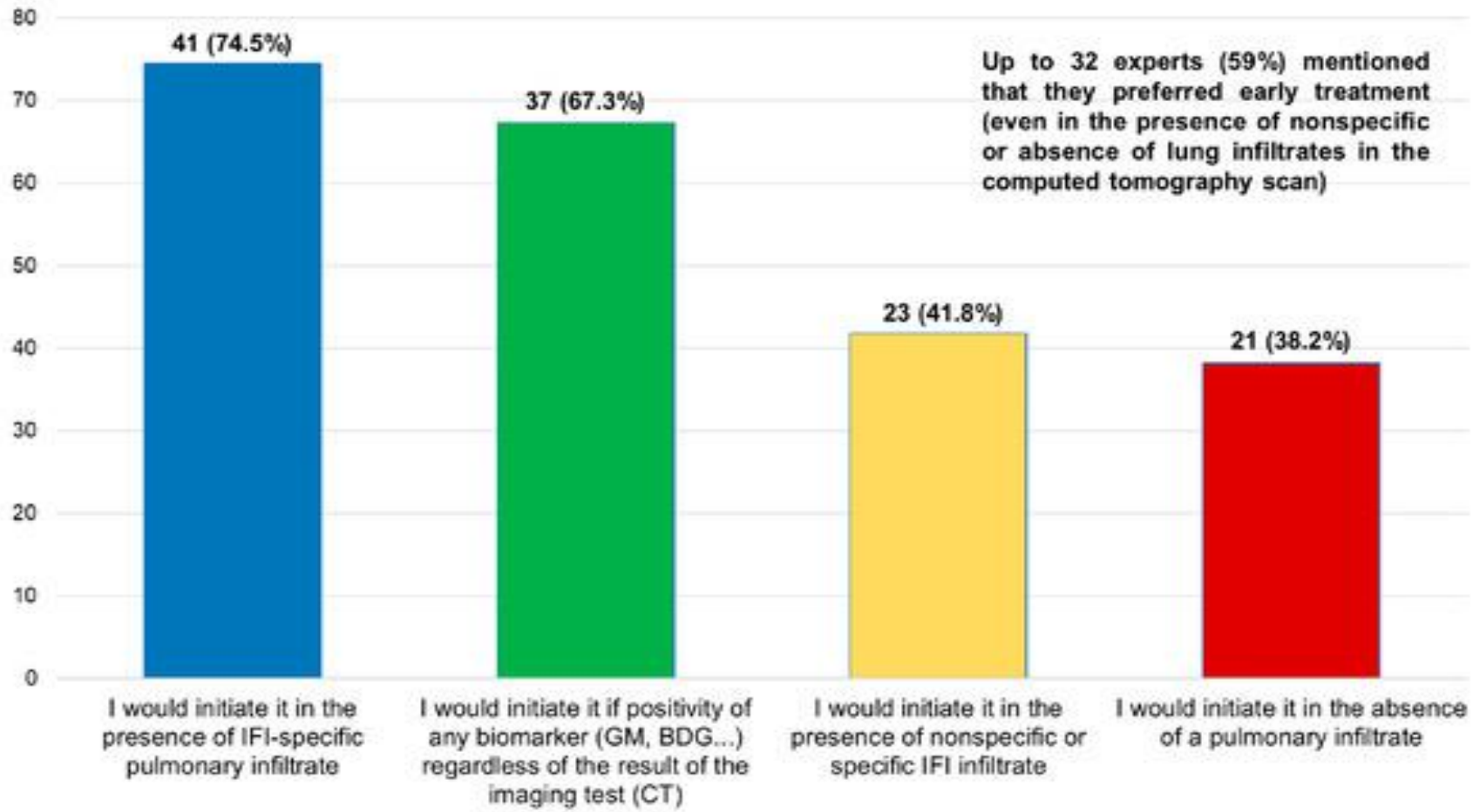
Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia

Philip A. Pizzo M.D. [1], K.J. Robichaud R.N. [1], Fred A. Gill M.D. [1], Frank G. Witebsky M.D. [1]

Epidemiology and sites of involvement of invasive fungal infections in patients with haematological malignancies: a 20-year autopsy study



Answers given to the question ”In the face of persistent febrile neutropenia (5 days), what would you do regarding antifungal treatment?”

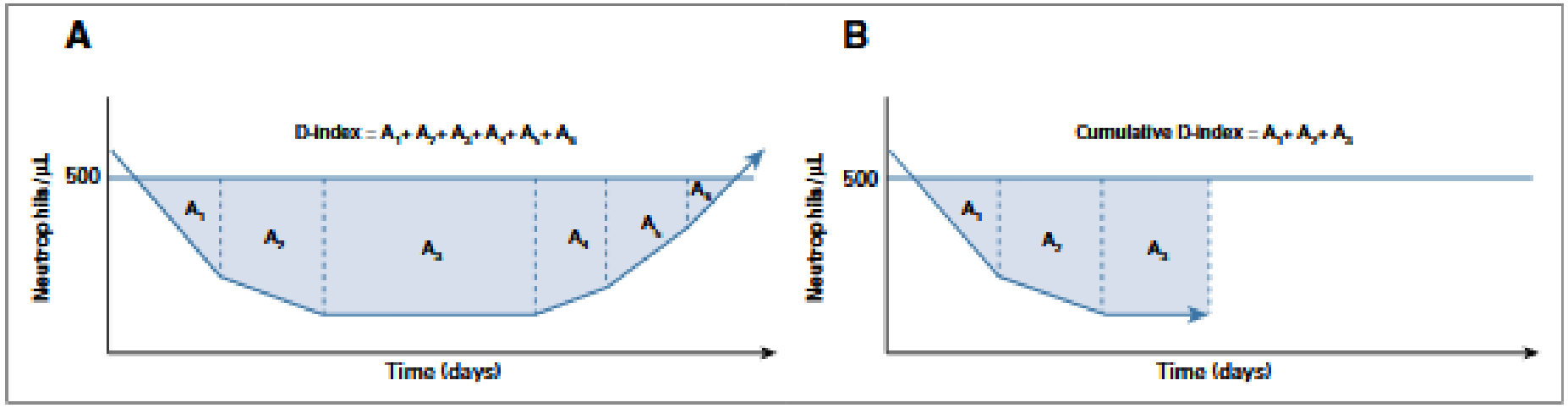


D-Index–Guided Early Antifungal Therapy Versus Empiric Antifungal Therapy for Persistent Febrile Neutropenia: A Randomized Controlled Noninferiority Trial

- The European Organisation for Research and Treatment of Cancer (EORTC) performed a randomized controlled trial to evaluate the efficacy of EAT with amphotericin B in patients with FN persisting for 4 days despite the use of broad-spectrum antibacterial therapy. There were 1 and 6 documented IFIs and 0 and 4 fatal IFIs in the EAT and no-EAT groups, respectively.
- On the basis of these results, guidelines recommend EAT for patients with FN persisting for 4 to7 days who are anticipated to have a neutropenic duration of>7 days.
- However, for most patients with persistent FN, EAT likely results in overtreatment. Therefore, preemptive antifungal therapy or **a diagnostic-driven approach has been investigated**, in which antifungal agents are started based on persistent FN with positive results of serum tests and/or imaging studies.
- These diagnostic tests target aspergillosis rather than candidiasis, because the
- incidence of aspergillosis is higher than that of candidiasis in the era of antifungal prophylaxis.

D-Index–Guided Early Antifungal Therapy Versus Empiric Antifungal Therapy for Persistent Febrile Neutropenia: A Randomized Controlled Noninferiority Trial

Portugal et al proposed a novel index, called the D-index, which is calculated as the area surrounded by the neutrophil curve and the horizontal line at a neutrophil count of 500/mL, to evaluate both the duration and severity of neutropenia.



Calculation of the (A) D-index and (B) cumulative D-index.

D-Index–Guided Early Antifungal Therapy Versus Empiric Antifungal Therapy for Persistent Febrile Neutropenia: A Randomized Controlled Noninferiority Trial

- CONCLUSIONA novel strategy, DET, decreased the use and cost of antifungal agents without increasing invasive fungal infections and can be a reasonable alternative to empiric or preemptive antifungal therapy.

Antifungal Strategy in Patients with Invasive Fungal Disease Associated with Hematological Malignancies Based on Risk Stratification

The incidence of IFD in patients with HMs has been rising in recent years due to the:

- Extensive use of chemotherapy
- Radiotherapy
- Broad-spectrum antibiotics
- Glucocorticoids
- Immunosuppressive agents
- Central venous catheterization
- Hematopoietic stem cell transplantation (HSCT)

Antifungal Strategy in Patients with Invasive Fungal Disease Associated with Hematological Malignancies Based on Risk Stratification

- For the empirical group, the antifungal treatment was initiated when broad-spectrum antibiotics given for 4–7 days were ineffective and fever persisted or when fever reoccurred after 4 or 7 days of antibiotics and there was no imaging or microbiological evidence of IFD. The antifungal therapy was continued until the patient's temperature returned to normal or clinical symptoms improved.

Antifungal Strategy in Patients with Invasive Fungal Disease Associated with Hematological Malignancies Based on Risk Stratification

- For the **diagnostic-driven treatment** group, antifungal therapy was initiated if any of the following conditions occurred, e.g., imaging examination suggesting pneumonia, acute sinusitis, stage III mucositis, or most importantly, septic shock, IFD-related skin damage, central nervous system symptoms with unknown etiology, liver or spleen abscess, severe diarrhea, colonization by Aspergillus, or positive (1, 3)-b-D-glucan (G test) and/or galactomannan tests (GM test). The antifungal therapy was continued until the patient's imaging changes disappeared or microbiological evidence became negative

Antifungal Strategy in Patients with Invasive Fungal Disease Associated with Hematological Malignancies Based on Risk Stratification

Results:

- A total of 458 HM cases were included in the study.
- 239 cases in the empirical treatment group and 219 cases in the diagnostic-driven treatment group.
- No significant difference in sex, age, primary disease.

Antifungal Strategy in Patients with Invasive Fungal Disease Associated with Hematological Malignancies Based on Risk Stratification

Risk Stratification and Effectiveness Comparison in the Empirical Therapy and Diagnostic-Driven Therapy

The effectiveness rate was 87.9% in the empirical treatment group and 81.7% in the diagnostic-driven group, and there was no significant difference between the two groups ($p \geq 0.05$)

Liposomal amphotericin B-the present

Liposomal amphotericin B has retained its place in the therapeutic armamentarium based on its clinical profile:

1. A broad spectrum of antifungal activity with a low risk of resistance
2. Predictable pharmacokinetics with a rapid accumulation at the infection site (including biofilms)
3. **A low** potential for drug-drug interactions
4. **A low** risk of acute and chronic treatment-limiting toxicities versus other formulations of amphotericin B
5. It is a suitable choice for the first-line empirical or pre-emptive treatment of suspected fungal infections in neutropenic haematology patients and is an excellent alternative for patients with documented fungal disease who can no longer tolerate or continue their first-line azole or echinocandin therapy, both in the haematology setting and in the ICU. Moreover
6. it is the first-line drug of choice for the treatment of invasive mucormycosis. Finally, liposomal amphotericin B is one of the few antifungal agents approved for use in children of all ages over 1 month and is included in paediatric-specific guidelines for the management of fungal disease

Liposomal amphotericin B-the present

- Based on the results of a randomized double-blind trial in which liposomal amphotericin B (as empirical therapy) showed similar efficacy compared with amphotericin B deoxycholate:

1. Fewer breakthrough fungal infections
2. Less infusion-related toxicity
3. Less nephrotoxicity, liposomal amphotericin B became the standard
4. Caspofungin showed a similar overall success rate to liposomal amphotericin B and thus fulfilled the statistical criteria of non-inferiority
5. The proportion of patients who survived at least 7 days after therapy was greater in the caspofungin group (92.6% versus 89.2%; P = 0.05).37 Based on the results of this trial, caspofungin was also approved for the empirical treatment of IFIs.

Liposomal amphotericin B versus conventional amphotericin B in the empirical treatment of persistently febrile neutropenic patients

- Of patients included in the pharmacoeconomic study, 18.7% of those receiving liposomal amphotericin B had renal toxicity compared with 66.3% of patients in the conventional amphotericin B arm.
- Patients that developed nephrotoxicity had significantly longer hospitalization compared with patients without nephrotoxicity (22.8 versus 15.8 days).
- Furthermore, total hospital costs were significantly higher.

Empiric treatment against invasive fungal diseases in febrile neutropenic patients: a systematic review and network metaanalysis.

- The most optimal antifungal agent for empiric treatment of invasive fungal diseases (IFDs) in febrile neutropenia is controversial.
- k meta-analysis showed that amphotericin B lipid complex, conventional amphotericin B, liposomal amphotericin B, itraconazole and voriconazole had a significantly lower rate of fungal infection-related mortality than no antifungal treatment.
- Caspofungin appeared to be the most effective agent for all-cause mortality and fungal infection-related mortality, whereas micafungin tended to be superior for treatment response.

Efficacy and Safety of Caspofungin Treatment in Febrile Neutropenic Patients with Hematological Disorders: A Multicenter Consecutive Case Series

Conclusion:

- These results suggest that the use of CAS in FN patients with hematological diseases is effective and well-tolerated, and we believe that the use of CAS could become a significant treatment in Japan.

The Value of Nasal and Oral Clinical Examination in Febrile Neutropenic Patients for Initiating Antifungal Therapy as a Preemptive Method

- The mortality rate differed significantly among the two groups; it was 7.5% in the preemptive group and 25% in the empirical group

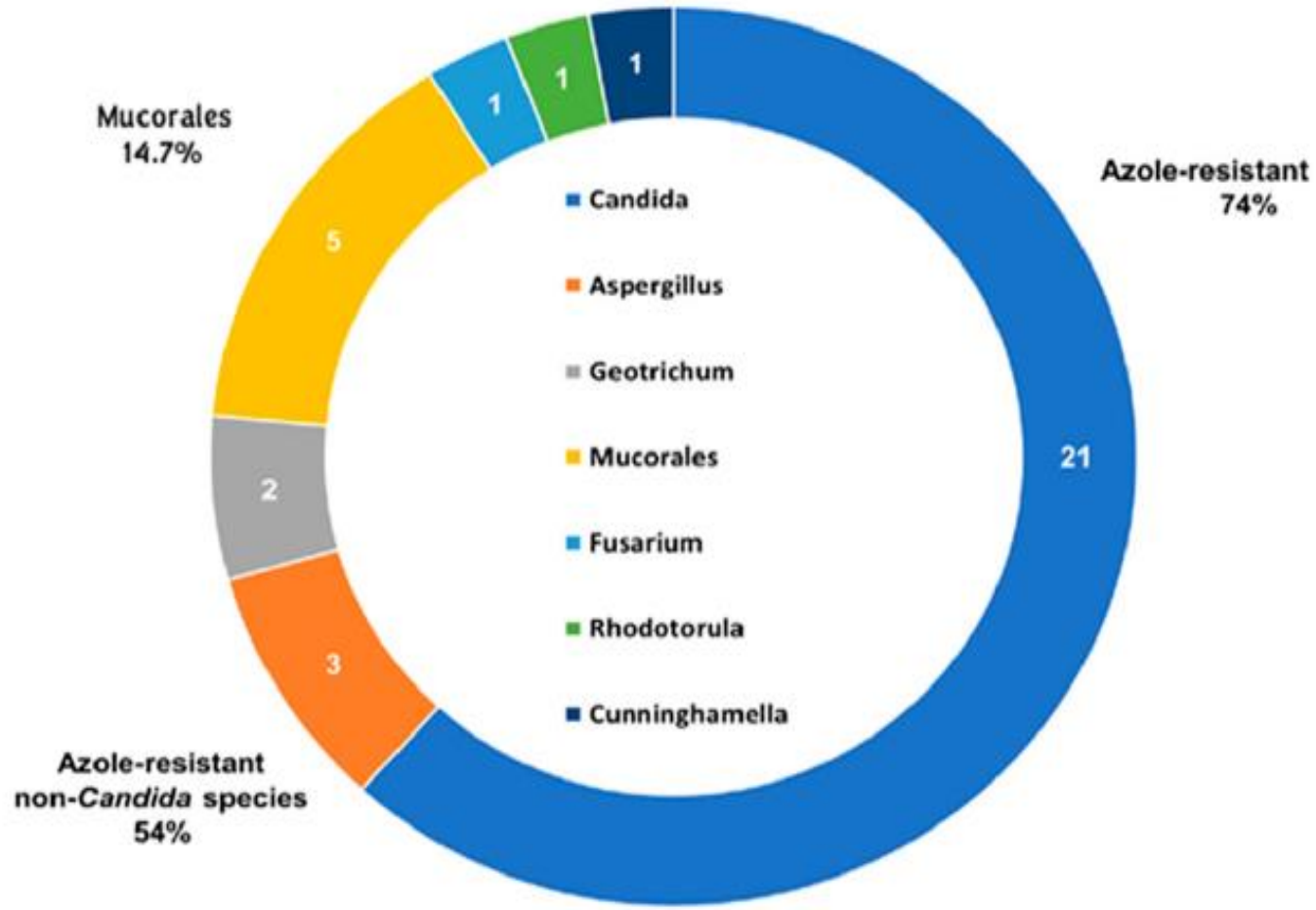
Conclusion:

- Daily oral and nasal cavities examination to find the symptoms of IFIs and then start preemptive antifungal agents may be able to lead to accurate diagnosis, earlier treatment, and decreasing sinus surgery debridement in leukemia patients with neutropenia.

IFISTRATEGY: Spanish National Survey of Invasive Fungal Infection in Hemato-Oncologic Patients

1. Recent advances in the treatment of hematologic malignancies have improved the overall survival rate
2. But the number of patients at risk of developing an invasive fungal infection (IFI) has Increased
3. Invasive infections caused by non-Candida albicans species, non-Aspergillus molds, and azole-resistant Aspergillus fumigatus have been increasingly reported in recent years

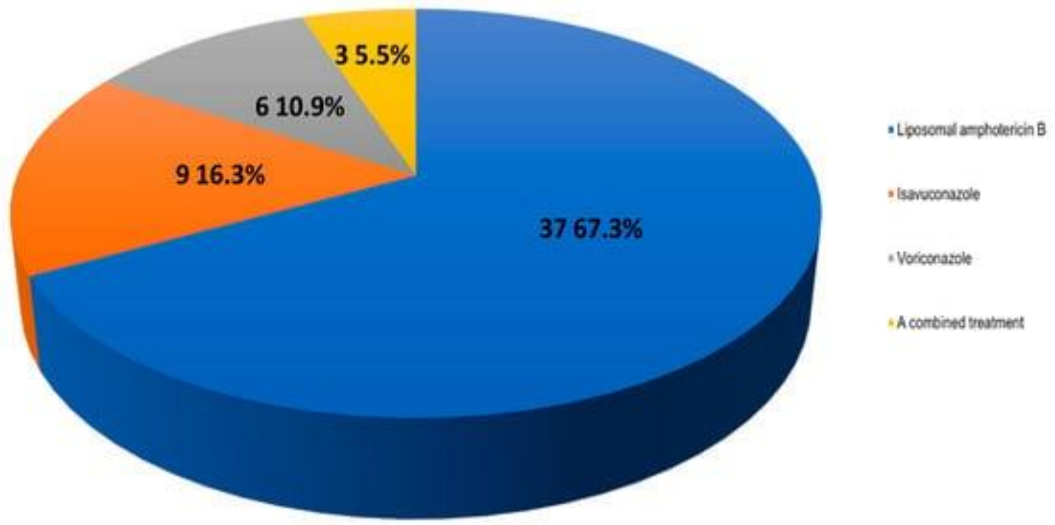
Epidemiology of proven breakthrough invasive fungal infections (IFI) in Spanish patients with hematologic malignancies



Breakthrough IFI in hematologic patients

- Antifungal susceptibility was tested in the Spanish National Center for Microbiology.
- A total of 121 episodes were included, with 41 cases of proven IFI (principally, 20 cases of non-*Candida albicans*, 7 cases of Mucorales, 3 cases of *Aspergillus*, and 2 cases of *Fusarium solani*).
- Overall, in 30.6% of patients there was IFI progression, and the mortality rate was 47.1%.
- The authors concluded that breakthrough IFIs were fundamentally caused by rare molds (Mucorales or *Fusarium* spp.), non-*fumigatus Aspergillus* and non-*Candida albicans* species, which were resistant to the prior antifungal drug administered,
- Finally, a retrospective analysis which compared 24 microbiologically documented breakthrough IFIs that occurred during posaconazole or voriconazole.

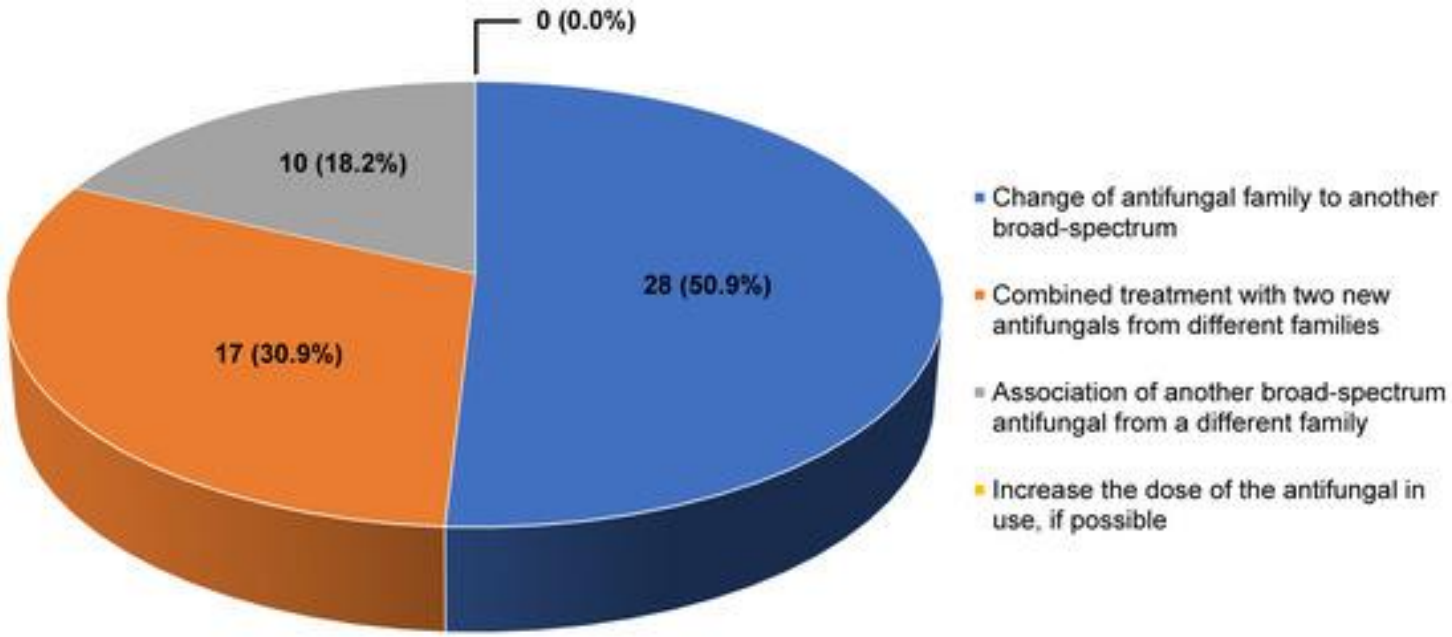
Answers to the question “If echinocandins were used as prophylaxis in a patient receiving midostaurin or venetoclax, in case of suspected breakthrough fungal infection, what treatment would you administer?”



Questionnaire and answers provided by the 55 experts who participated in the survey

	Answers n (%)
1-Do you consider it most likely that you will find yourself facing a case of secondary resistance to a broad-spectrum antifungal?	
▪ who after a period of improvement presents clinical worsening attributed to his fungal infection	17 (31.5)
▪ Patient who does not respond to early antifungal treatment administered for 10 days	16 (29.6)
▪ Patient on antifungal prophylaxis who debuts with symptoms that do not respond to broad-spectrum antibiotics	15 (27.8)
▪ Who does not respond to early antifungal treatment	6 (11.1)
2-In the event of suspected resistance in a patient receiving treatment for aspergillosis, what strategy would you carry out?	
Change of antifungal family to another broad-spectrum	28 (50.9)
Combined treatment with two new antifungals from different families	17 (30.9)
Association of another broad-spectrum antifungal from a different family	10 (18.2)
Increase the dose of the antifungal in use, if possible	0 (0.0)

Answers provided by the experts to the question “In the event of suspected resistance in a patient receiving treatment for aspergillosis, what strategy would you carry out?”



Management of patients with hematologic malignancies and HSCT, who are at risk of developing IFIs

Based on these results, we can conclude that most of the experts agree on:

- (1) if resistance of *Aspergillus* to azoles is suspected, switching to another broad-spectrum antifungal family such as L-AMB would be the best option; (2) early antifungal treatment is the best option in case of persistent febrile neutropenia (even in the presence of nonspecific or absence of lung infiltrate in the CT);
- (3) for antifungal drugs failing to reach adequate levels during the first days, and if IA is suspected, the most appropriate strategy would be the association of an antifungal of another family;
- (4) there was no consensus on which prophylaxis (broad-spectrum azoles or echinocandins) should be used in patients receiving new targeted therapies, such as midostaurin and venetoclax;
- (5) L-AMB was the preferred option in case of breakthrough IFIs in patients receiving new targeted therapies and prophylactic therapy with echinocandins.

Empiric treatment against invasive fungal diseases in febrile neutropenic patients: a systematic review and network metaanalysis.

Conclusion:

- A previous systematic review in 2008 showed that the addition of empiric antifungal therapy in patients with FN significantly improved IFDs outcomes compared to no antifungal.
- The 2016 IDSA published guidelines stratify FN patients based on presumed duration and severity of neutropenia, as well as other co-morbidities.
- Empiric antifungal therapy is recommended in high-risk patients for IFD who have persistent fever after 4–7 days of broad-spectrum antibacterials and no identified infection source .
- Despite a significant number of published guidelines regarding the treatment of IFD, recommendations fail to reach a consensus on preferred antifungal therapy in patients with FN.

Thank you for your attention